

A Case of Autoimmune Hepatitis during Brodalumab Treatment for Psoriasis

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Autoimmune hepatitis (AIH) is a chronic inflammation of the liver caused by hepatocyte-specific autoantigens. Psoriasis is a chronic inflammatory skin disease characterized by a skewed interleukin-17 immune response and dysregulated epidermal hyperproliferation and differentiation. Patients with psoriasis have a higher risk of AIH. Some evidence indicates that AIH is triggered by treatment with certain drugs. Brodalumab is a human monoclonal antibody against interleukin-17 receptor A and is used to treat psoriasis. A 70-year-old Japanese man with psoriasis had elevated serum levels of transaminases and bilirubin, positive antinuclear antibodies, and high serum IgG levels after 11 months of brodalumab treatment. Histological analysis of liver tissue revealed interface hepatitis with lymphoplasmacytic infiltration. AIH was diagnosed and treated with prednisolone, which improved his symptoms. This is the first case of AIH during brodalumab treatment for psoriasis. The relationship between brodalumab and AIH should be further examined, and the risk of AIH in psoriatic patients treated with brodalumab should be carefully considered. (*J Nippon Med Sch* 2020; 87: 359–361)

Key words: autoimmune hepatitis, psoriasis, brodalumab, interleukin-17 receptor A

Introduction

Psoriasis is a chronic inflammatory skin disease characterized by an interleukin-17 (IL-17)-skewed immune response and dysregulated epidermal proliferation and differentiation¹. Psoriasis is strongly associated with autoimmune diseases such as inflammatory bowel disease, diabetes², and autoimmune hepatitis (AIH). A Danish nationwide cohort study reported that the incidence rate ratios of AIH in mild and severe psoriasis were 2.64 and 3.05, respectively².

AIH is characterized by chronic inflammation of the liver in the presence of histological interface hepatitis, hypergammaglobulinemia, and circulating autoantibodies³. AIH is putatively caused by diminished tolerance against autologous liver tissues and is initiated by aberrant CD4+ T cells that recognize hepatocyte-specific autoantigens. Approximately 9% of AIH cases are triggered by treatment with drugs, including minocycline and nitrofurantoin^{3,4}. Cases of AIH triggered by anti-tumor necrosis factor- α (TNF- α) therapies for psoriasis have recently been reported⁵. Brodalumab is a human

monoclonal antibody against IL-17 receptor A (IL-17RA) and has been used to treat psoriasis. It blocks the effects of IL-17 family cytokines, which include IL-17A, IL-17C, and IL-17E, and thus effectively suppresses inflammatory responses caused by these cytokines in psoriatic skin lesions. Herein, we present the first case of AIH associated with brodalumab treatment for psoriasis.

Case Report

A 70-year-old Japanese man with a 5-year history of psoriasis visited our department of dermatology for evaluation of scaly erythematous patches on his forearms, elbows, lower legs, knees, and back. The psoriasis area and severity index (PASI) score was 4.9 (**Fig. 1**). Despite treatment with a topical corticosteroid for 1 month, the eruption grew larger and worsened (PASI score, 10.8). Brodalumab (210 mg) was then injected subcutaneously at 0, 1, and 2 weeks, and every 2 weeks thereafter. The treatment improved his symptoms, and the PASI score improved to 2.4 at week 16. At 11 months of treatment, 9 days after an injection, he was admitted to the department of gas-

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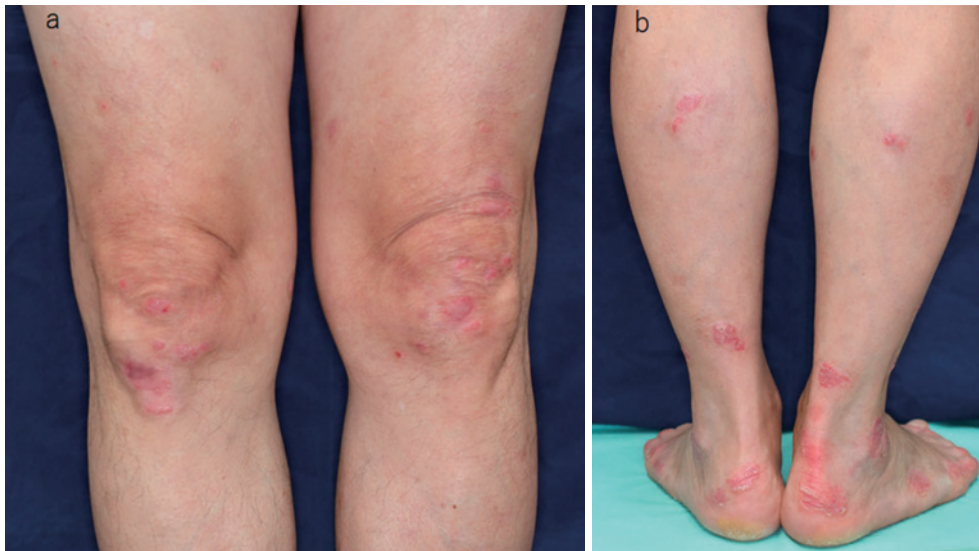


Fig. 1 Scaly erythematous patches on the knees (a) and ankles (b).

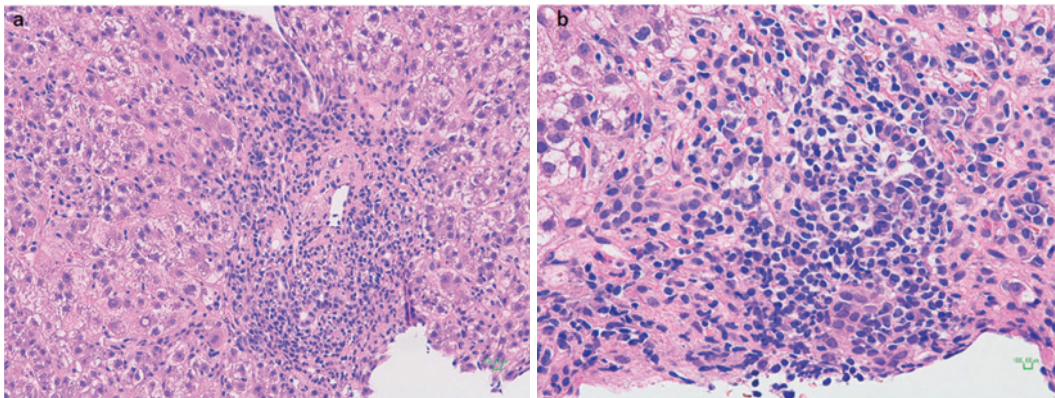


Fig. 2 (a) Liver biopsy specimen showing intense portal and periportal lymphoplasmacytic infiltration and interface hepatitis (hematoxylin and eosin, $\times 200$). (b) Prominent plasma cell infiltration is visible (hematoxylin and eosin, $\times 400$).

troenterology with jaundice, nausea, and general fatigue.

Although he was not a habitual drinker, laboratory tests revealed abnormal findings in liver function testing, namely, aspartate aminotransferase 1,293 IU/L (normal 13-33 IU/L); alanine aminotransferase, 1,462 IU/L (normal 8-42 IU/L); alkaline phosphatase, 477 IU/L (normal 115-359 IU/L); γ -glutamyl transferase, 175 IU/L (normal 10-47 IU/L); total bilirubin, 12.1 mg/dL (normal 0.2-1.3 mg/dL); direct bilirubin, 9.3 mg/dL (normal 0.1-0.4 mg/dL); and negative markers for hepatitis A, B, C, and E. Serum IgG was elevated at 2,325 mg/dL (normal 870-1,700 mg/dL), and antinuclear antibodies (1:40; homogeneous and speckled pattern) were weakly positive. He was negative for anti-liver-kidney microsomal antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies. A liver biopsy revealed portal and periportal

lymphoplasmacytic infiltrates with active interface hepatitis (Fig. 2). In accordance with the simplified diagnostic criteria for AIH³, the definite diagnosis was AIH (7 points). Brodalumab treatment was thus discontinued, and he was treated with prednisolone (30 mg/day) and ursodeoxycholic acid (600 mg/day). Serum levels of liver enzymes and IgG normalized after 2 weeks of treatment, and serum bilirubin levels normalized after 4 weeks. Antinuclear antibodies, however, remained positive.

Discussion

The precise mechanisms underlying AIH pathogenesis remain unclear. However, recent studies suggest that an imbalance between regulatory T cells (Tregs) and T helper (Th) 1/Th17 cells contributes to the pathogenesis of AIH⁶. In the liver of AIH model mice and peripheral

blood of AIH patients, expressions of IL-17A and interferon- γ (IFN- γ) were increased and the number of Tregs was decreased⁶. Because psoriasis is also associated with enhanced activities of Th1/Th17 cells and decreased Treg activity, the pathogenesis of AIH and psoriasis may be similar. Psoriatic patients may thus be more susceptible to AIH than the reference population. Tissue-resident memory T cells in skin and liver may be common mediators of psoriasis and AIH⁷.

Our patient developed AIH during brodalumab treatment for psoriasis. Other cases of AIH triggered by drugs have been reported⁴. Covalent binding of a drug or its metabolite to hepatocellular proteins may form adducts, which may present as neoantigens that induce an autoimmune inflammatory response⁴. The pathogenesis of drug-induced AIH may also involve host-specific factors, such as specific HLA types or abnormalities in drug-metabolizing enzymes, proinflammatory effector cells, and Tregs⁴. Some studies reported that AIH was triggered by anti-TNF- α antibodies, like infliximab and adalimumab, in psoriatic patients⁸. The interval between antibody initiation and AIH onset ranges from 2 weeks to 2 years (median 3 months), but the rate of AIH in psoriasis patients treated with anti-TNF- α antibody has not been reported. In addition to immune-mediated mechanisms, anti-TNF- α antibodies antagonize the effects of TNF- α in inducing cytotoxic T cells, which normally eliminate autoreactive B cells. This could result in proliferation of autoreactive B cells and lead to production of autoantibodies against hepatocellular autoantigens⁵. In contrast, there have been no reported cases of AIH induced by anti-IL-17RA or anti-IL-17A treatment. Although it is uncertain whether brodalumab triggered AIH in the present case, brodalumab treatment might have unmasked latent AIH, to which patients with psoriasis are susceptible. One possible mechanism involves brodalumab-induced suppression of IL-17 family cytokines, which may have conversely enhanced Th1 cell activity and triggered an autoimmune inflammatory response in the liver. A recent study reported the pathogenic role of aberrantly activated and expanded Th1 cells that produce TNF- α in AIH⁹. In addition, IL-17 family cytokines, especially IL-17A and IL-17E, suppressed differentiation of Th1 cells, and blocking of IL-17RA effectively suppressed the effects of IL-17A, IL-17E, and IL-17E, promoted the expression of TNF- α and IFN- γ in the liver, and aggravated liver damage in mice infected with *Trypanosoma cruzi*¹⁰.

In conclusion, we described the first case of AIH during brodalumab treatment for psoriasis. The relationship

between brodalumab and AIH should be further studied, and the risk of AIH in patients with psoriasis treated with brodalumab should be carefully considered.

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Conflict of Interest: The authors declare no conflicts of interest.

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